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TRANSMITTAL FORM

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First Named Inventor	John Joseph HARRINGTON
Art Unit	1632
Examiner Name	J. T. Woitach
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ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
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- [ ] Information Disclosure Statement
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Date	June 30, 2006	Reg. No.	56,126

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Docket No.: ATX-007CP4DV12
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
John J. Harrington *et al.*

Application No.: 09/484,331

Confirmation No.: 9576

Filed: January 18, 2000

Art Unit: 1632

For: COMPOSITIONS AND METHODS FOR NON-TARGETED ACTIVATION OF ENDOGENOUS GENES

Examiner: WOITACH, Joseph T.

APPELLANT'S RESPONSE TO EXAMINER'S ANSWER

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellant files this response to Examiner's Answer to an appeal brief mailed May 3, 2006, from the U.S. Patent and Trademark Office.

This response contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I.	Real Party In Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Invention
VI.	Grounds of Rejection to be reviewed on appeal
VII.	Argument
VIII.	Claims Appendix
IX.	Evidence Appendix
X.	Related Proceedings Appendix

I. Real Party in Interest

Appellant thanks the Examiner for acknowledging the real party of interest in this appeal.

II. Related Appeals, Interferences, and Judicial Proceedings

Appellant thanks the Examiner for acknowledging that there are no other appeals, interferences or judicial proceedings known to Appellant which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. Status of Claims

Appellant thanks the Examiner for indicating that the status of the claims contained in the appeal brief filed by the Appellant is correct.

IV. Status of Amendments

Appellant thanks the Examiner for indicating that the Appellant's status of amendments contained in the appeal brief is correct.

V. Summary of Invention

Appellant thanks the Examiner for indicating that the summary of claimed subject matter contained in the appeal brief is correct.

VI. Grounds of Rejection to be Reviewed on Appeal

Appellant thanks the Examiner for acknowledging that the Appellant's statement regarding the grounds of rejection to be reviewed on appeal is correct.

VII. Argument

Appellant responds herein to the Examiner's Points (9) and (10) in the Examiner's Answer. Appellant submits that with respect to the grounds of rejection which the Appellant had already responded to during the prosecution of the above-identified patent application, the Appellant has not provided any further comments. Appellant, however, responds to any new grounds of rejection raised by the Examiner in the Examiner's Answer.

Appellant notes that in the Examiner's Answer, rather than specifically address the Appellant's evidence directly, the Examiner has adopted a new rationale. The Examiner admits that the claimed steps would be inherent in the terms "drug discovery" but then alleges that the person of ordinary skill in the art would not have recognized that these steps would apply to Appellant's cells because these cells are "artificially generated." (*See*, Examiner's Answer at page 5). The Examiner further states at page 4

> Methods using cells and purified proteins in identifying compounds as potential drug candidates are known and used in the art, however, the cells and purified proteins used represent well-characterized systems and/or targets for screening purposes. Further, generally gene trap vectors are also known in the art, and are used commonly as research tools to identify or characterize the consequence of altering gene expression in a cell. However, there is no nexus nor guidance provided in the instant specification, nor in the art of record, for providing an artificially

> generated cell representing an uncharacterized system and identifying compounds as potential drug candidates.

Accordingly, it appears that the Examiner is adopting a new position by alleging that the disclosure of using Appellant's cells for drug discovery would not have reasonably conveyed to the person of ordinary skill in the art that the claimed method steps applied to the Appellant's cells. Appellant disagrees for the reasons that follow.

First, the Dhanoa Declaration directly refutes this position. Dr. Dhanoa has explained how the person of ordinary skill in the art would have recognized the claimed steps and their application to the Appellant's cells.

Second, this position is scientifically untenable. The Appellant's cells are no more artificial than recombinant cells expressing an exogenous gene. Such cells were routinely used in the art for compound screening in the drug discovery process. Therefore, in the context of compound screening, both types of cell are interchangeable. Please also see page 6 of the Applicant's Response filed August 28, 2000, where this particular point was explained to the Examiner.

A. Written Description

On page 4 of the Examiner's Answer the Examiner further states that the specification "fails to provide literal or even general support for the method of 'drug discovery' wherein the test compound is exposed to the purified protein." First, Appellant brings this Examiner's attention to the fact that Examiner Reynolds previously acknowledged support for this very embodiment in the instant application, in an interview on June 2, 2003.. Accordingly, this embodiment was not at issue, rather it was whether there was support for exposing RAGE *cells* to candidate compounds. Furthermore, Appellant submits that the specification provides more than general support for a method of drug

discovery where a test compound is exposed to the purified protein. See, for example, at least at page 7, lines 29-31 of the specification, which states "[t]he expression product can then be isolated and purified to use, for example, in protein therapy ***or drug discovery***." (***emphasis added***).

B. Enablement

On page 5 of the Examiner's Answer, the Examiner alleges that there is not a single example of use of any cell in drug discovery. Appellant again points out that drug discovery had been routinely practiced on cells expressing exogenous genes as well as on cells naturally expressing a gene. Therefore, it would have been reasonably predictable that any cell expressing a desired gene, endogenous or exogenous, could be used in the method without an undue burden of experimentation. The Examples in the specification show that virtually any desired endogenous gene could be activated with Appellant's methods. Therefore, a person of ordinary skill would have reasonably predicted that Appellant's cells, expressing a desired gene, would be useful in the claimed methods without undue experimentation. They would not have even needed an example in the specification to reach that conclusion.

Further, on page 5 of the Examiner's Answer, the Examiner bases the rejection on the position that Appellant's cells are "products not normally found in nature, effectively an artificial generated system." Once again, Appellant points out that recombinant cells expressing exogenous genes are not normally found in nature either. Yet, these cells were routinely used for drug discovery. Accordingly, contrary to the Examiner's statement on page 6 of the Examiner's Answer, *i.e*, "there is no basis for using an artificially generated

system, in this case a gene activated by gene trap vector [sic] in drug discovery," there was more than adequate basis for using an artificially generated system.

On page 6 of the Examiner's Answer, the Examiner states "[f]or drug discovery, the skilled artisan requires art accepted models or at least a well characterized system associated with something to make it a relevant system for drug discovery. In this case, the use of gene trap vectors to generate cells that are not normally found in nature representing an artificial and uncharacterized system [sic]." This statement is not consistent with the fact that in drug discovery, random compounds are tested against *any* gene and *any* phenotype. Any desired gene or phenotype is subject to such screening as long as there is a cell available that expresses that gene or that phenotype. Appellants are not discussing *optimizing* compounds, delivering compounds to patients, assessing compounds in disease models and the like.

The Examiner ultimately concludes "[i]n the context of the claimed invention where the gene is activated and protein expression is increased, even the specific proteins listed fail to provide art accepted targets for gene discovery." The Examiner discusses two specific instances. First, the Examiner speculates that the Appellant's cells expressing insulin would not be useful for drug discovery because insulin is underexpressed in diabetes. This is erroneous. It is immaterial whether insulin is underexpressed or overexpressed in a cell used in a method for identifying a candidate compound that affects insulin expression. Accordingly, expressing insulin in Appellant's cells is useful to assay for compounds that affect insulin expression. As an example, a compound that increases insulin expression is a potential therapeutic compound. The Examiner then discusses clotting factors. The same rationale applies to clotting factors. Expressing a clotting factor in Appellant's cells can be used to assess compounds that affect the expression of clotting factors. Accordingly, Appellant disagrees with the Examiner's ultimate conclusion.

In conclusion, Appellant notes that the Examiner now has taken a new position. It is stated on page 7 of the Examiner's Answer: "[t]he heart of the instant rejection focuses on the nature of the invention and that the method as claimed provides for an artificially generated system for use in gene discovery." This position has no evident scientific basis as long as one believes that the data in Appellant's specification demonstrate that Appellant's methods will provide cells expressing virtually any desired gene.

The Examiner points out on page 8 of the Examiner's Answer, that original claims 1-57 did not have the terms "drug discovery." Appellant believes that this is not relevant to their arguments. In the final Office Action, the Examiner had asserted that this phrase was inserted into the claims in response to a rejection under 35 USC §102. However, as Appellant had pointed out in the Appeal Brief, claims 58-62 were not amended in response to an art rejection. Claims 58-62 were mistakenly referred to as the "original" claims since they were the first set of claims submitted for examination. Accordingly, the term "drug discovery" was not added to the claims in response to a prior art rejection

On page 9 of the Examiner's Answer the Examiner states "[t]he office would acknowledge that methods of drug discovery are generally knows [sic] and practiced in the art (as summarized the Bennani Declaration page 3-4)." But the rejection is based on the absence of a "nexus for such 'drug discovery' methodology and the system in which they are practiced as provided in the instant specification." *See,* Examiner's Answer at page 10. The Declarations are now considered to be unpersuasive because they are "critically flawed." "The critical flaw in both declarations and the disclosure of the present specification is that the art does not recognize cells generated by the random insertion of a gene trap vector which results in the activation of an endogenous gene to be a system for drug discovery".

See, Examiner's Answer at page 10. Appellant agrees herewith the Examiner's understanding.

Appellant notes that the claimed invention is novel. Therefore, how could the art have recognizes it? However, once the cells are disclosed as being useful for drug discovery, the person of ordinary skill immediately appreciates the Appellant's invention. This is what the Dhanoa Declaration, and, to some extent the Bennani Declaration, points out. Just because a cell is new does not mean that the person of ordinary skill would not understand immediately how it should be used in a prior art process. Thus, the Declarations have been dismissed improperly as follows "[t]he Declarations have not been found convincing because they fail to provide a nexus between the general methods of drug discovery known in the art at the time of filing and the artificial system generated by RAGE technology provided by the instant specification to support that the method steps instantly claimed are 'inherent'." *See*, Examiner's Answer, page 10. Appellant points out that the Dhanoa Declaration clearly states that the person of ordinary skill would immediately have recognized that Appellant was providing this nexus by relating their cells to drug discovery.

The new basis for the enablement rejection appears to be the same basis as for the written description rejection, *i.e*, that there is no "nexus" between drug discovery and the Appellant's cells. The Examiner acknowledges that "in some drug screening assays compounds are practiced without knowing anything about what is being applied/tested." Examiner's Answer, page 11. Appellant assumes that by the statement the Examiner means that in some drug screening assays compounds are exposed to cells before the testers know if there is a relationship between the compound and the gene or phenotype being tested. Appellant notes that in drug discovery methods, the vast number of compounds are tested

without any knowledge of how these compounds will affect the gene expression or phenotype because the compounds are merely off the shelf. This is explained in the Bennani Declaration.

The Examiner summarizes the position as follows

> The office would acknowledge that methods of making a cell using a gene trap vector and methods of drug discovery are generally known and practiced in the art. ***The issue at hand is whether the specification provides the necessary guidance to combine these two technologies/methodologies.*** More specifically, does a cell generated by random insertion of an activating promoter that upregulates an endogenous gene provide a tool the artisan could predictably use without undue experimentation.

(***emphasis added***). As discussed above, Appellant asserts that the answer to the Examiner's question is yes. The Appellant's cells expressing an activated endogenous gene would have been expected to be interchangeable with a recombinant cell expressing an exogenous gene *when it comes to compound testing*. This is because all one needs to test a compound is a cell expressing a gene or a phenotype. It is immaterial whether that expression occurs by exogenous or endogenous means. Both cells are equally amenable to the drug discovery process.

On page 13 of the Examiner's Answer, the Examiner states the following "[t]here is no art of record where gene trap vectors were used to generate materials for drug discovery, or that effectively uncharacterized cells with an interesting and a desired phenotype serves as the basis of a model system for drug discovery." Appellant points out that there should be no such art of record because this is a novel combination. Moreover, there is no scientific reason given for asserting that an undue burden of experimentation would have been

required to test a compound against a "uncharacterized cell with an interesting and a desired phenotype".

The Examiner asserts "[e]ssentially, what is required is that the artisan establish that cell or isolated protein as an appropriate target for drug discovery." What does it mean to establish a cell or establish a protein as an appropriate target? Any desired protein and any cell expressing that protein is appropriate. If the artisan is interested in finding a compound that affects expression of a specific protein, then that is the appropriate target for that researcher.

In the end it comes down to the Examiner's erroneous conclusion that the claims are not enabled because the specification does not provide a nexus between the Appellant's cells and drug testing. "In this case, the novel aspect of the invention would be the use of gene trap vectors to generate materials for drug discovery. Such an invention requires an undue amount of empirical experimentation without an [sic] reasonable expectation of success to establish the material as appropriate for use in methods of drug discovery." *See*, Examiner's Answer, page 14.

Appellant respectfully disagrees. Appellant's cells would be just as likely to provide a target for drug discovery as cells expressing proteins from exogenous DNA. Both types of cell express a desired protein (phenotype). Both cells allow the artisan to expose the cell to a compound and assay for the effect of the compound on expression of any desired gene (phenotype). Accordingly, Appellant's cells would have been reasonably expected to be equally amenable to the drug discovery process, *i.e*, could be used without undue burden of experimentation.

VIII. Claims Appendix

Claims appendix was provided with the Appeal Brief, therefore, it is not filed with this paper.

IX. Evidence Appendix

Appellant has no evidence to file with this paper, therefore no evidence appendix is included.

X. Related Proceedings Appendix

As stated above in II, no related proceedings are referenced herein and copies of decisions in related proceedings are not provided, hence no related proceedings Appendix is included.

Appellant believes no fee is due with this paper. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. ATX-007CP4DV12 from which the undersigned is authorized to draw.

Dated: June 30, 2006

Respectfully submitted,

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